Poster 125TiP

Phase 1 Study of Patritumab Deruxtecan (HER3-DXd) in Patients With Advanced *KRAS* G12C Non-Small Cell Lung Cancer: Study U102 Cohort 5

Luis Paz-Ares,[1] Conor Steuer,[2] Gerrina Ruiter,[3] Makoto Nishio,[4] Haruyasu Murakami,[5] Dong-Wan Kim,[6] Enriqueta Felip,[7] Christina S. Baik,[8] Chien-Chung Lin,[9] Erminia Massarelli,[10] Myung-Ju Ahn,[11] Xin Su,[12] Masahiro Fujimura,[12] Leena Pasupuleti,[12] Ariel E. Aguilo,[12] Stephen Esker,[12] Helena A. Yu,[13] Hidetoshi Hayashi,[14] Pasi A. Jänne[15]

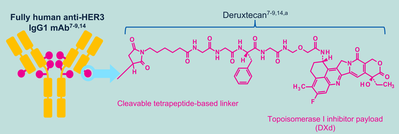
[1]Hospital Universitario 12 de Octubre, Spanish National Cancer Research Center, Universidad Complutense and CIBERONC, Madrid, Spain; [2]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [3]Netherlands Cancer Institute, Amsterdam, the Netherlands; [4]The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; [5]Shizuoka Cancer Center, Shizuoka, Japan; [6]Seoul National University College of Medicine and Seoul National University Hospital, Seoul, Republic of Korea; [7]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [8]Thoracic, Head and Neck Medical Oncology, Fred Hutchinson Cancer Center, University of Washington School of Medicine, Seattle, WA, USA; [9]National Cheng Kung University Hospital and Tainan Hospital, Ministry of Health and Welfare, Tainan, Taiwan; [10]The University of Texas at Tyler School of Medicine, Tyler, TX, USA; [11]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [12]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [13]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [14]Kindai University Hospital, Osaka-Sayama, Osaka, Japan; [15]Dana-Farber Cancer Institute, Boston, MA, USA

BACKGROUND

- The *KRAS* G12C mutation is a common oncogenic driver in NSCLC, observed in approximately 14% of NSCLC cases, with a lower frequency observed in Asian patients[1,2]
  - Based on promising results, the KRAS G12C inhibitors sotorasib and adagrasib have both received accelerated approval for patients with advanced *KRAS* G12C–mutated NSCLC who have received ≥1 prior therapy[3,4]
  - However, limited treatment options exist following disease progression on KRAS inhibitors
- HER3 is expressed across a variety of solid tumors, including NSCLC, in which it has been reported in 83% of primary tumors[5]
  - HER3 expression in NSCLC has been associated with poor clinical outcomes, including metastatic progression and decreased relapse-free survival[5]
  - Preclinical data have demonstrated increased HER3 expression following KRAS inhibition[6]
- HER3-DXd is an antibody-drug conjugate composed of a human anti-HER3 monoclonal antibody linked to a topoisomerase I inhibitor payload via a stable tetrapeptide-based, tumor-selective, cleavable linker (**Figure 1**)[7-9]
- U31402-A-U102 (NCT03260491) is an ongoing, multicenter, phase 1, dose-escalation/expansion study of HER3-DXd in pretreated patients with NSCLC[10-12]
- Previous results in patients with *EGFR*-mutated NSCLC (from cohorts 1 and 3) demonstrated a manageable safety profile of HER3-DXd and promising efficacy[12]
  - cORR by BICR, 41%; median PFS, 6.4 months; median OS, 16.2 months[12]
- Confirmed response by BICR was observed in 3 of 5 patients with *KRAS/NRAS* mutations from a cohort without common *EGFR*-activating mutations (cohort 2),[a] suggesting that HER3-DXd may be an effective therapy for these patients[13]
- Based on these results, cohort 5 was designed to evaluate the antitumor activity as well as the pharmacokinetics, efficacy, and safety of HER3-DXd in patients with *KRAS* G12C–mutated NSCLC following progression on targeted therapy

[a] The common *EGFR*-activating mutations excluded from cohort 2 were Ex19del, L858R, L861Q, and G719X.

Figure 1. HER3-DXd Structure and Attributes



[a] The clinical relevance of these features is under investigation. [b] Refers to the linker and payload. [c] Based on animal data.

THE 7 KEY ATTRIBUTES OF HER3-DXd

The **mAb** directs the DXd ADC to the tumor cell.

1. High drug-to-antibody ratio ≈8[7,14,b]

The **linker** binds the mAb to the payload.

2. Plasma-stable linker-payload[7-9,14,b]
3. Tumor-selective cleavable linker[7-9,14,15,b]

The **payload** induces cell death when delivered to the tumor.

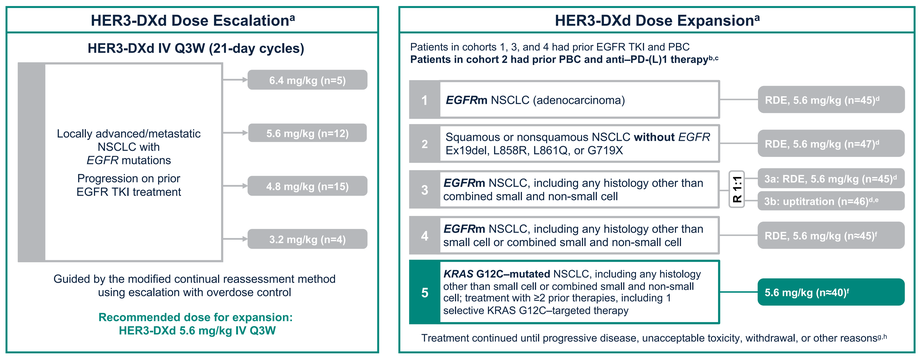
4. Topoisomerase I inhibitor[7-9,14,b]
5. High potency[7-9,14,b]
6. Short systemic half-life[7,8,b,c]
7. Bystander antitumor effect[7,16,b]

Corresponding author: Luis Paz-Ares
Contact: lpazaresr@seom.org

METHODS

- Cohort 5 was designed to evaluate the efficacy and safety of HER3-DXd in patients with locally advanced or metastatic NSCLC harboring a *KRAS* G12C mutation after failure of ≥2 systemic therapies, including an inhibitor targeting this genomic alteration
- Forty patients whose tumors contain a *KRAS* G12C mutation will be recruited (**Figure 2**)
- Eligibility criteria and study objectives are summarized in **Tables 1** and **2**, respectively

Figure 2. U31402-A-U102 Cohort 5 Study Design



[a] Patients with stable brain metastases were permitted to enroll. A tumor biopsy was required prior to study entry, but patients were not selected for inclusion based on measurement of HER3 expression. [b] Unless unable or unwilling to receive immunotherapy. [c] Patients with known targetable genomic alterations (other than *EGFR* mutations) for which therapy was available must have had ≥1. [d] Drug product manufactured by the clinical manufacturing sites. [e] Uptitration regimen: cycle 1, 3.2 mg/kg; cycle 2, 4.8 mg/kg; cycle 3 and subsequent cycles, 6.4 mg/kg. [f] Drug product manufactured by the commercial manufacturing sites. [g] Other reasons for discontinuation may include investigator discretion, death, pregnancy, study termination by sponsor, and loss to follow-up. [h] The number of treatment cycles is not predetermined for cohort 5.

Table 1. Key Eligibility Criteria

Inclusion Criteria

- Age ≥18 years
- Locally advanced or metastatic NSCLC with ≥1 measurable lesion (per RECIST version 1.1)
- Histologically or cytologically documented squamous or nonsquamous NSCLC
- Availability of sufficient quantity of pretreatment tumor tissue sample
- ECOG PS of 0 or 1
- *KRAS* G12C mutation detected from tumor tissue or liquid biopsy
- ≥2 prior systemic therapies for locally advanced or metastatic disease, including 1 selective KRAS G12C–targeting therapy[a]
- Adequate bone marrow reserve and organ function

Exclusion Criteria

- Evidence of small cell or combined small cell and non-small cell histology in the original tumor
- Prior targeted therapy for any genomic alteration other than *KRAS* G12C
- History of ILD that required treatment with corticosteroids or current or suspected ILD/pneumonitis
- Clinically severe respiratory compromise
- Clinically significant corneal disease
- Spinal cord compression or clinically active CNS metastases, defined as untreated and symptomatic or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms
- Any evidence of severe or uncontrolled diseases (eg, active bleeding diatheses, active serious infection)
- Prior therapy with an anti-HER3 antibody or any antibody-drug conjugate containing an exatecan derivative that is a topoisomerase I inhibitor
- Unresolved toxicities from prior anticancer therapies
- Prior history of other, different active malignancy ≤3 years prior to enrollment

[a] Including as part of a clinical trial (for example, the combination of KRAS G12C–targeted therapy and immuno-oncology therapy can be considered as 2 prior systemic therapies).

Table 2. Study Objectives

Primary Endpoint

- Antitumor activity
  - ORR by BICR[a]

Secondary Endpoints

- Safety and tolerability
  - AE profile and physical examination findings (including ECOG PS)
- Immunogenicity and pharmacokinetics
  - Serum concentrations and pharmacokinetic parameters for anti–HER3-ac-DXd, total anti-HER3 antibody LC-MS, and DXd in the full pharmacokinetic sampling cohort
- Antitumor activity characteristics
  - ORR by investigator assessment[a]
  - DCR, DOR, TTR, and PFS by both BICR and investigator assessment
  - OS
- PROs
  - NSCLC-SAQ score; change in total score and proportion of patients with deteriorated/stable/improved symptoms
  - PRO-CTCAE; proportion of patients with deteriorated/stable/improved symptoms
- Association between HER3 protein expression and HER3-DXd efficacy

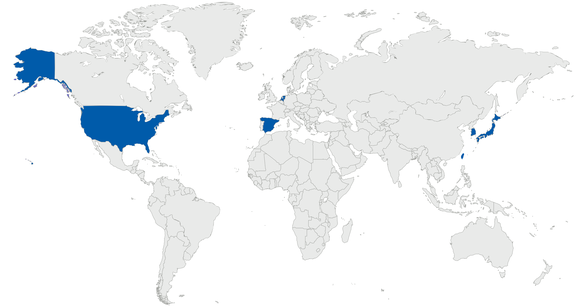
Exploratory Endpoints

- Intracranial antitumor activity
  - ORR by BICR[b]
- Association between biomarkers and HER3-DXd clinical activity
  - Correlation of efficacy with tumor and plasma biomarkers (which may include genomic alterations, gene expression, gene signatures, and cfDNA genomic alterations)

[a] Per RECIST 1.1. [b] Per CNS RECIST.

Enrollment Status

- A total of 40 patients are planned to be enrolled in sites spanning North America (USA), Europe (Spain and the Netherlands), and Asia (Japan, Republic of Korea, and Taiwan)
- Cohort 5 enrollment began 27 February 2024, with the study expected to last 5 years from the time of the first patient's signed consent form[a]



[a] The overall study duration may be extended if additional cohorts are incorporated.

ABBREVIATIONS

ADC, antibody-drug conjugate; AE, adverse event; BICR, blinded independent central review; cfDNA, cell-free DNA; CNS, central nervous system; cORR, confirmed objective response rate; DCR, disease control rate; DOR, duration of response; DXd, topoisomerase I inhibitor payload; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; Ig, immunoglobulin; ILD, interstitial lung disease; IV, intravenous; KRAS, KRAS proto-oncogene, GTPase; LC-MS, liquid chromatography–mass spectrometry; mAb, monoclonal antibody; NRAS, NRAS proto-oncogene, GTPase; NSCLC, non-small cell lung cancer; NSCLC-SAQ, Non-Small Cell Lung Cancer Symptom Assessment Questionnaire; OS, overall survival; PBC, platinum-based chemotherapy; PD-(L)1, programmed cell death 1 (ligand 1); PFS, progression-free survival; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; Q3W, every 3 weeks; R, randomization; RDE, recommended dose for expansion; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; TTR, time to response.

DISCLOSURES

L. **Paz-Ares** has served on advisory boards for Roche, MSD, Bristol Myers Squibb, AstraZeneca, Lilly, Pfizer, PharmaMar, Bayer, Amgen, Janssen, GSK, Novartis, Takeda, Sanofi, Mirati, Genomica, Altum Sequencing, BeiGene, Daiichi Sankyo, and Medscape; has received travel funding and/or speaker honoraria from AICME, CCO, Boehringer Ingelheim, STAb Therapeutics, Daiichi Sankyo, AstraZeneca, MSD, Bristol Myers Squibb, Janssen, Novartis, Roche, Sanofi, Amgen, Tesaro, Alkermes, Lilly, Takeda, Pfizer, PharmaMar, and Cantargia; is a shareholder in STAb Therapeutics; is a member of AACR, ASCO, AECC, and ESMO; is a board member of Genomica, Altum Sequencing, and AECC; and is President of the Fundación OncoSur and ASEICA.

ACKNOWLEDGMENTS

Medical writing support was provided by Simon Foale, PhD (Nucleus Global, an Inizio company), and was funded by Daiichi Sankyo Company, Limited and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Editorial support was provided in accordance with Good Publication Practice guidelines (https://ismpp.org/gpp-2022).

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Presented at: European Lung Cancer Congress 2025; 26-29 March 2025; Paris, France. Poster 125TiP.